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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/473,872 12/28/99 YOON

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HM12/0621

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EXAMINER

BRUNOVSKIS, P

ART UNIT

PAPER NUMBER

1632

DATE MAILED:

06/21/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/473,872

Applicant(s)

Yoon

Examiner

Peter Brunovskis

Group Art Unit

1632

☐ Responsive to communication(s) filed on _____

☐ This action is FINAL.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 35 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) 1-40 is/are pending in the application

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) 1-40 is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been received.

☐ received in Application No. (Series Code/Serial Number) _____

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 7

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

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DETAILED ACTION

Specification

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). However, this application fails to comply with all of the requirements of 37 CFR 1.821 through 1.825. The specification and drawings disclose numerous nucleotide sequences which have not been identified by an appropriate SEQ ID NO. Moreover, it is difficult to determine whether all of these sequences are recited in the "Sequence Listing".

37 CFR 1.821(d) states: "[w]here the description or claims of a patent application discuss a sequence that is set forth in the "Sequence Listing" in accordance with paragraph (c) of this section, reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description of claims, even if the sequence is also embedded in the text or the description or claims of the patent application.

Applicants are required to comply with all of the requirements of 37 C.F.R. §§ 1.821 through 1.825. Any response to this Office Action which fails to meet all of these requirements will be considered non-responsive. The nature of the noncompliance with the requirements of 37 C.F.R. §§ 1.821 through 1.825 did not preclude the examination of the application on the merits, the results of which are communicated below.

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The disclosure is objected to because of the following informalities: There are multiple instances where Applicant has failed to properly provide a trademark designation in the context of reciting use of "cytofectin" (e.g. p. 38). Applicant is advised to review the application include "TM" where appropriate.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the stable genetic modifications" in line 4. There is insufficient antecedent basis for this limitation in the claim.

Claim 1 and 18 (and dependent claims) are indefinite in their recitation of "locations" in line 2 since it is not clear what this refers to-cells, skin, or tyrosinase gene. Also, the method steps do not clearly relate back to the preamble, since the method steps recite phenotypic changes to the skin whereas the preamble recites a method for modifying a selected gene in cells of a

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human or animal skin and does not clearly recite whether the method involves direct delivery to the skin of a human or whether it embraces delivery to human cells in culture which can then be grafted onto the human or animal skin of an individual "result[ing] in phenotypic changes at said locations of the skin". Additionally, it is unclear what "effective amount" (line 2) refers to (effective for what?), what structural limitations apply to "chimeric RNA-DNA oligonucleotide", nor is it clear how "naturally expressed" is contextually defined, or whether "naturally expressed" is directed to a "selected gene" prior to genetic modification, subsequent to genetic modification, or to *any* human or animal gene that is capable of being naturally expressed in skin cells independent of whether it has been genetically modified.

Claims 8 and 23 are indefinite in their recitation of "the region" since it is unclear what constitutes "the region[s]" metes and bounds and whether "the region" is limited to the contiguous deoxynucleotides or whether it can encompass any of the flanking ribonucleotides.

Claims 8 and 23 recite the limitation "the site of modification" in part (b), line 11. There is insufficient antecedent bases for this limitation in the claims.

Claims 8-10 and 23-25 are indefinite in their recitation of "nuclease protected" since it is unclear how this term is defined or how the limitation applies to the "one or more nucleotides" (e.g. under what circumstances, what nuclease?). Further, it is unclear whether the first and second strings are contiguous.

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Claims 9 and 24 recite the limitations "the two strands" in step (b), lines 9 and 10, respectively; and "the site of modification" in part (b), line 12 and 13, respectively. There is insufficient antecedent bases for this limitation in the claims.

Claims 9, 10, 24, and 25 (part b) are indefinite in their recitation, "has nucleotides in the first string and second strings that are" since it is unclear *which* nucleotides in "has nucleotides" are being referred to (e.g. *all* except the mismatched base pair or just a portion?).

Claims 10 and 25 (part b, line 5) are indefinite in their recitation of "the same number of deoxynucleotides" since it is unclear whether the area comprising "the same number of deoxynucleotides" in the second string is paired to fully complementary deoxynucleotides in a homologous (corresponding) region of the first string or whether the second string merely has "the same number" distributed along the entire length of the second string. Step (b) of claims 10 and 25 are also indefinite in their recitation, "one, two or four pairs of nucleotide insertion or deletions" since it is unclear what "deletions" is directed to--one string relative to the other string of the chimeric oligonucleotide or both strings relative to the two strands of the selected gene. Also, it is not clear how to resolve the difference between the first and second strings being fully complementary with the exception of one mismatched base pair on the one hand, but *also* being fully complementary to a segment of the selected gene except for the "one, two, or four pairs of nucleotide insertions or deletions" on the other.

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Claim 32 is indefinite for failing to clearly relate how the "treatment" results in the skin disorder of the animal model. Specifically, it is not clear whether the skin disorder is due to the oligonucleotide or something else in the composition.

Claims 34-39 are indefinite in their recitation of "[t]he method" since it not clear what method[s] are being referred to; base claims 32 and 33 and not drawn to methods, but compositions (i.e. animal model).

Claim 40 is indefinite in its recitation of "locations" in line 2 since it is not clear what this refers to--cells, skin, or tyrosinase gene.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 2-7, 19, 32, 33, and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

An adequate written description of a DNA (or gene) or animal model requires more than a mere statement that it is part of the invention and reference to a potential method for isolating or developing it; what is required is a description of the DNA or animal model itself. It is not sufficient to define a DNA or animal model solely by their gene names or principal biological

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property, i.e. skin disorder, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA or animal model with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid or an animal model, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNAs or animals that share a genetic relationship or phenotype, respectively, without defining the means for isolating or obtaining them is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Adequate description of the methods first requires an adequate description of the materials, i.e. specific DNA sequences (i.e. genes), animals, and which provide the means for practicing the invention.

The specification recites a series of chimeric RNA-DNA oligonucleotides (RDOs) targeted to human and mouse Tyr, CL7A1, and KRT17. There is no evidence of record that Applicants were in possession of gene sequences for any more than these six alleles. Moreover, the only RDOs explicitly disclosed are those containing T-loop containing "dumbbell" structures. However, the claimed RDOs do not recite these structures, but rather recite a much broader

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genus of RDOs that does not comprise these structural limitations. Furthermore, although several proposed chimeric oligonucleotides targeted to cytokines were disclosed (i.e. IL-1 β , IL-1 α , TNF- α), it was not disclosed whether these were targeted to humans, mice or other animals.

Additionally, the specification does not provide an adequate written description concerning the mutations which form the basis for designing the RDOs to target the broad range of genes recited in claims 4, 19, and 33, for example. In the absence of these gene sequences (or references to them) and the mutations which would result in a phenotypic change, such as those leading to broad range of phenotypes embraced by e.g. albinism, epidermal fragility disorders, and keratinization disorders (as in claims 17 and 31), and their gene sequence homologs and mutations for all of the animals to which the claims are drawn, the instant disclosure does not provide an adequate written description that is commensurate in scope with the methods and compositions (i.e. animal models) of the claimed invention.

Claims 1-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for creating stable genetic modifications in the skin of mice comprising genetic and phenotypic alteration in mouse tyrosinase, COL7A1, and KRT17 genes *using specific RDOs disclosed in the working examples*, does not reasonably provide enablement for methods for making and using stable genetic modifications in the skin of humans and other animals comprising genetic and phenotypic alterations involving the broad scope of genes recited in the claims. The specification does not enable any person skilled in the art to which it pertains,

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or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The factors to be considered in determining enablement are summarized In re Wands 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir, 1988). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation....Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Factors that can be used in evaluating undue experimentation include: the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims.

Applicant and others have recently reported partial genetic correction in animal models of several different diseases, including hemophilia, Duchenne muscular dystrophy, and Crigler-Najjar syndrome type I using chimeric RNA-DNA oligonucleotides (RDO). The claimed invention recites use of RDO in methods for correcting or introducing mutations in selected genes associated with various skin disorders in human or animal skin which result in phenotypic changes at the locations in which the RDOs are introduced. Applicant has provided working examples which demonstrate that RDOs can be used to provide partial genetic correction of albinism in the skin of mice treated with a tyrosinase-targeted chimeric oligonucleotide and to create dominant

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mutations in skin tissues of mice resulting from treatment with RDOs targeting mouse COL7A1 (MCOL7-A RDO; Fig. 6) and KRT17 (MKRT17-A RDO; Fig. 7) genes (Example 4, p. 40-41). While all three of these oligonucleotides led to point mutation alterations, only the tyrosinase-targeted RDOs contain an embedded string of contiguous deoxyribonucleotides flanked by ribonucleotides opposite the second string solely comprised of deoxyribonucleotides (e.g. Fig. 1, Example 1, p. 37-39). Applicant has not provided any working examples which support the notion that insertions or deletions can be similarly introduced in skin, either in the case comprising RNA strings interrupted by deoxyribonucleotides (as in Example 1) or with RDOs comprising an RNA-only string capable of pairing with a DNA-only string (as in Example 4).

The technology disclosed is not routinely accomplished in the art, nor is it yet known how applicable the animal results to proposed experiments in other species (or other tissues or required target cells). In spite of the enthusiasm for this recently developed approach to genetic modification, a number of skilled artisans remain cautious; Stephenson recently reported that "many laboratories have been unsuccessful in getting the technique to work or have achieved only modest rates of gene conversion (JAMA, vol. 281(2), Jan. 13, 1999, p. 120). Michael Strauss, a skilled artisan recently commented on this technology as follows: "[m]any researchers (including our group) have since applied this technology to their gene of interest and most of them have failed so far" (Nature Med. vol. 4, March 1998, p. 275, middle of left column) and continues by saying: "[t]he paper by Kren et al. Is both very inspiring and very controversial. It should be regarded as the initial venture into developing molecular tools for site-specific correction of

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certain gene rather than as a complete kit for the correction of all genetic defects" (p. 275, bottom paragraph, middle column). The inability of multiple groups to duplicate the results of just one or two laboratories suggests the need for a better understanding of the mechanism involved in this process, but more importantly, the key RDO structures and method steps that would enable one of skill in the art to practice this technology as broadly as is claimed. It is not readily apparent from the specification what critical features are responsible for the limited successes reported in the art.

The physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In light of the unpredictability of the physiological art, and in particular that of site-specific genetic modification/correction, there is a proportionately greater burden for enablement.

Applicant has previously stated on the record that "it's not clear why the efficiency of the procedure, using the same cells and the same chimeric molecule, varies so widely (Stephenson, JAMA, 281(2), p. 120, left column, last paragraph). Moreover, as quoted in Stephenson, Applicant Yoon states that: "[b]ecause factors such as recombination frequency, cell cycle, and

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other elements vary among cell types, it may not be possible to apply the technology to all cells (p. 120, middle column, top paragraph). Given the unpredictability of this art there is not a reasonable expectation of success for a broader extension of the results disclosed in the working examples of the specification to either genetic modification in human skin or to targeting of other genes, particularly wherein the etiology and target cells are not well understood, and wherein multiple, qualitatively different RDO substrates are envisioned. For example, there is no evidence on record to suggest that *human* skin comprises a cell type that has the appropriate criteria cited by the Applicant above to enable the practice of the claimed invention. Furthermore, it is not clear what limitations exist concerning the specific types of mutations that can be introduced into skin or what specific RDO substrates are amenable for in vivo genetic modification in skin. For example, there is no evidence of record to suggest that insertions or deletions can be introduced in skin using Applicant's methodology. While the specification offers a clear invitation to experimentation, it does not provide an enabling disclosure for targeting of the broad set of genes and host species that are recited in the genes. It is not clear from the specification, for example, whether the range of animals cited indeed manifest all of the same genetic disorders as recited in Table 1. Further there is no evidence to suggest e.g. that humans, mice, rabbits, goats, monkeys, pigs, and cows even carry all the affected genes cited in Table 1, nor does the disclosure provide sufficient guidance for one of skill in the art how to apply the broad range of RDOs envisioned to make and use the broad range of animal models that are embraced by the scope of the claims. For example, the claimed RDO embodiments are much broader in scope than the actual RDOs which

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are disclosed in the specification, all of which comprise T-loop "dumbbell" structures. The specification does not give sufficient guidance teaching skilled artisans how to make or use the broad range of RNA-DNA structures that are embraced by the generic claims of the instant application. Furthermore, although the working examples appear to demonstrate phenotypic changes, there is not sufficient guidance concerning what threshold levels of correction are required to generate a phenotypic change, what constitutes a [measurable] phenotypic change within the context of the broad range of genetic disorders recited, or what mutations will result in such changes (either to correct genetic defects or introduce them). Without guidance concerning the mutations resulting in these phenotypic changes, one of skill in the art cannot even begin to design the appropriate RDOs, much less test them.

Given the unpredictable and undeveloped state of the art as described above, it would likely require undue experimentation for one skilled in the art to appropriately develop the claimed invention for genetic modification according to the broad scope of the claimed subject matter. This is particularly true given the state of the art, the nature of the invention, the unpredictability of the art, the scarcity of guidance and working examples commensurate in scope with the broad scope of the claimed subject matter, and the amount of experimentation necessary.

Certain papers related to this application may be submitted to Art Unit 1632 by facsimile transmission. The FAX number is (703) 308-4242 or 305-3014. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6(d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained by applicant or applicant's representative. NO

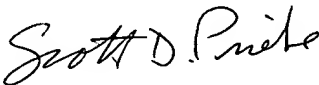
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DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Peter Brunovskis whose telephone number is (703) 305-2471. The examiner can normally be reached on Monday through Friday from 8:30 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jasmine Chambers, Ph.D. can be reached at (703) 308-2035.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Peter Brunovskis, Ph.D.
Patent Examiner
Art Unit 1632


SCOTT D. PRIEBE, PH.D.
PRIMARY EXAMINER